Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease

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Background: Intranasal ketorolac challenges can induce respiratory reactions in patients with aspirin-exacerbated respiratory disease (AERD).

Objective: To determine whether intranasal ketorolac challenges might be used for aspirin desensitization.

Methods: One hundred patients with suspected AERD who were referred to Scripps Clinic from May 1, 2007 to December 31, 2009 were challenged with 4 increasing doses of ketorolac intranasally at 30-minute intervals. Symptoms, objective changes in the results of their nasal examination, peak nasal inspiratory flow rates, and forced expiratory volume in 1 second (FEV_1) values were recorded. After nasal ketorolac dosing, patients were given oral aspirin as part of the challenge and desensitization. A control group consisted of 100 patients who had previously undergone our standard oral aspirin challenges and desensitization. Both groups were consecutively enrolled and had similar clinical characteristics.

Results: Compared with the standard oral aspirin challenge and desensitization, intranasal ketorolac and modified aspirin challenge significantly attenuated the mean percentage decrease in FEV_1 values (8.5% vs 13.4%; $P = .01$) and decreased the percentage of extrapulmonary reactions (23% vs 45%; $P = .002$), particularly laryngospasm (7% vs19%; $P = .02$) and gastrointestinal reactions (12% vs 33%; $P = .001$). This new protocol was significantly shorter, lasting an average of 1.9 vs 2.6 days ($P = <.001$). In fact, 83% of the patients completed the new protocol in less than 48 hours compared with only 20% in the oral challenge control group ($P < .001$).

Conclusions: Intranasal ketorolac challenge and desensitization followed by rapid oral aspirin challenges is effective, safe, and less time-consuming than our standard oral aspirin desensitization protocol.

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INTRODUCTION

Therapeutic and management options of aspirin-exacerbated respiratory disease (AERD) are either complete avoidance of cyclooxygenase 1–inhibiting drugs or aspirin desensitization and continuous aspirin therapy. Studies have shown that desensitization and treatment with aspirin can significantly improve symptoms and quality of life, decrease formation of nasal polyps, decrease the number of sinus infections, and reduce the need for systemic corticosteroids and sinus surgery in patients with AERD.[1–3] Despite the benefits of oral aspirin desensitization, the procedure is time-consuming and has the potential to provoke severe bronchospasm and extrapulmonary adverse effects in some patients. These 2 factors remain barriers to more widespread use of aspirin desensitization in a number of patients with suspected AERD.

In Europe, intranasal lysine-aspirin is used as a diagnostic and therapeutic agent for AERD[4,5]; however, lysine-aspirin is not available in the United States. Therefore, a US study of intranasal ketorolac was performed, which revealed that ketorolac is a safe and effective alternative for diagnosing AERD.[6] In this study by White et al,[6] several patients had no subsequent reactions to oral aspirin challenges (OACs) immediately after a positive ketorolac challenge result. This result led to the hypothesis that intranasal ketorolac desensitization might be possible. Because ketorolac is given locally to the nasal membrane, we theorized that patients might have a response limited to the upper airways and potentially have less systemic reactions.

METHODS

Participants and Inclusion and Exclusion Criteria

One hundred consecutive patients, from May 1, 2007 to December 31, 2009, with a clinical history suggestive of AERD were referred to Scripps Clinic for aspirin challenge and desensitization. All patients who met the study criteria were offered the combined intranasal ketorolac and aspirin protocol or standard OAC. Inclusion criteria included the following: age of 18 years or older, baseline forced expiratory

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volume in 1 second (FEV_1) greater than 1.5 L or more than 60% predicted, and ability to generate flow through a peak nasal inspiratory flow (PNIF) meter. Exclusion criteria included complete nasal obstruction (ie, usually secondary to nasal polyps), pregnancy or lactation, history of stomach ulcers, bleeding disorders, or treatment with warfarin. The protocol was approved by the Institutional Review Board/Human Subjects Committee.

Patients continued to take their usual controller medications, including inhaled, intranasal, and systemic corticosteroids, long-acting bronchodilators, and leukotriene-modifying drugs (LTMDs). The use of antihistamines and decongestants was discontinued 48 hours before the protocol to prevent masking of the histamine-induced symptoms of rhinitis and conjunctivitis. Use of a short-term β-agonist on the morning of challenge was also an exclusion criterion.

If the patient was not already taking an LTMD, we recommended taking either montelukast or zileuton 2 weeks before desensitization for any patient. Provocative reactions included any upper and/or lower respiratory tract symptoms and signs consistent with conjunctivitis, rhinitis, laryngospasm, and bronchospasm or decrease in nasal flow rate ($\geq$20%) and/or FEV_1 ($\geq$15%).

Our primary end point was to evaluate and compare efficacy and safety of intranasal ketorolac and aspirin as a means of desensitization in AERD with a control group who had undergone OAC. Our secondary end point was to compare the time in days that each protocol required to achieve aspirin desensitization. Successful aspirin desensitization was defined as 3 hours after ingesting aspirin, 325 mg, and experiencing no symptoms, changes in nasal flow rates, or decrease in FEV_1 values.[7]

Oral Challenge Control Group

The control group consisted of 100 consecutive patients who were referred to Scripps Clinic for possible AERD, from 2003 to 2004, who all underwent standard OACs.[8] These patients had similar clinical characteristics, they used the same controller medications, and their challenges or desensitization antedated any investigations with intranasal ketorolac. The starting doses of aspirin were 20 or 45 mg, with 3-hour intervals between doses and advancing doses of 60, 100, 150, 325, and 650 mg. Before the 2009 study by Hope et al,[7] which demonstrated that desensitization was completed in all AERD patients after tolerating a 325-mg dose of aspirin, dosing continued until a final tolerance of aspirin, 650 mg, was achieved. Therefore, for appropriate comparison with this current study, the time after 650 mg was deleted and all calculations regarding time taken to complete desensitization ended 3 hours after taking aspirin, 325 mg.[7]

Materials

Ketorolac tromethamine (60 mg/2 mL; American Pharmaceutical Partners Inc, Schaumburg, Illinois) was diluted with preservative-free normal saline, 2.75 mL, and mixed in an empty spray bottle (Nasacort AQ; Sanofi-Aventis, Bridgewater, New Jersey), producing a 4.75-mL volume of 12.6 mg/mL of ketorolac (Table 1). One spray actuated 0.1 mL, equivalent to 1.26 mg of ketorolac administered per spray. Aspirin in varying doses (30, 45, 60, 100, 150, and 325 mg) were prepared by a local compounding pharmacy. The PNIF meter (In Check Nasal; Clement Clarke International, Essex, England) was used to evaluate nasal flow, with measurements in liters per minute. At the discretion of the supervising physician, patients were treated at the time of their reactions symptomatically, using antihistamines, decongestant, mast cell stabilizers (eye drops), bronchodilators by nebulization, corticosteroids, epinephrine, nebulized racemic epinephrine, antiemetics, and acid-suppressing medications.

Table 1. Steps to Prepare Ketorolac Nasal Spray

1. Take ketorolac tromethamine (60 mg/2 mL) and preservative-free normal saline (2.75 mL).
2. Mix in an emptied spray bottle.
3. Prime with 5 sprays before use, then each spray actuates 1.26 mg of solution.
4. Instruct patient and medical personnel to tilt head down while spraying and sniff gently to avoid swallowing solution.

Procedure for Intranasal Ketorolac Challenge and Desensitization

All study participants signed informed consent forms and intravenous access was obtained. A questionnaire was completed, which included the baseline characteristics of age, sex, sinus infections per year, total sinus operations to date, history of polyps and physician-diagnosed asthma, current medications, and whether condition was atopic. In addition, patients were given a smell score based on their ability to smell before the challenge and desensitization, which was scored as follows: 0, complete anosmia; 1, partial intermittent anosmia; 2, partial continuous smell; 3, complete intermittent smell; and 4, normal sense of smell. Study participants underwent complete physical examinations, vital sign measurement, PNIF measurement, and spirometry. During challenges, participants were given a nasal grade for the objective signs assessed by physical examination and rhinoscopy, based on their reaction to ketorolac and/or aspirin (0, clear or normal; 1, partial congestion; 2, complete congestion; 3 = 2 plus conjunctivitis; 4 = 3 plus periorbital edema).

On day 1, study participants were challenged with incremental doses of ketorolac sprays every 30 minutes with accompanying PNIF measurement and spirometry before each dose. If patients showed signs or symptoms of a reaction, they were treated symptomatically. Once symptoms resolved, the provoking dose was repeated. Because of the possibility of a delayed or silent desensitization, even if no further reaction occurred, the full 4 escalating doses were completed and the patient waited a total of 60 minutes before proceeding to OAC. After completing the ketorolac nasal challenges, the first oral dose of aspirin was 60 mg. The patient was then monitored for 90 minutes (with spirometry

and measurement of PNIF rates performed regularly). If no reaction, the 60-mg dose was repeated. The second dose was not given if the patient reacted to the first dose of aspirin or until symptoms had completely resolved. The patients were discharged 90 minutes after the second aspirin dose if there was no reaction. This accelerated dosing protocol was established with the hypothesis that by using the nasal ketorolac protocol, patients with a negative ketorolac challenge result would be less likely to react to oral aspirin or would require a higher provoking dose.

On day 2, if there was no reaction to the 2 doses of 60 mg of aspirin on day 1, the patients received 150 mg of aspirin and 325 mg of aspirin 3 hours apart. For those patients who reacted to the second 60-mg dose of aspirin, the dose was repeated before proceeding to the 150-mg dose. Monitoring parameters were stable at baseline of day 2 and repeated throughout the day. A comparison of the 2 protocols is given in Table 2. Most patients were discharged by early afternoon of day 2.

Statistical Analysis

All data were entered in Microsoft Excel and analyzed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). Data were inspected for distribution, outliners, and normality before pursuing further analyses. Baseline characteristics were compared between patients in the intranasal ketorolac and aspirin challenge and OAC groups. Two-sample t tests were used to compare continuous variables. χ^2 Tests were used to compare categorical variables (1, yes; 0, no).

Outcome variables, including the presence of reactions and extrapulmonary adverse effects, were compared between AERD patients in the intranasal ketorolac and aspirin challenge and OAC groups. Two-sample t tests were used to compare continuous outcome variables, including percentage decrease in FEV_1 values and duration of desensitization. χ^2 Tests were used to compare categorical outcome variables, including the presence of a naso-ocular reaction, a more than 15% decrease in FEV_1 as a surrogate for bronchial reaction severity, an extrapulmonary reaction, and the duration of the procedure ($\leq$2 vs $>$ 2 days). All statistical analyses were 2-sided and considered significant if $P < .05$.

Table 2. Comparison of Standard Oral Aspirin and Modified Nasal Ketorolac Timeline[a]

Time	Oral aspirin challenge	Intranasal ketorolac and aspirin challenge
Day 1		
8 AM	20–40 mg	1 spray (1 in 1 nostril)
8:30 AM		2 sprays (1 in each nostril)
9 AM		4 sprays (2 in each nostril)
9:30 AM		6 sprays[b] (3 in each nostril)
10:30 AM		60 mg of aspirin
11 AM	40–60 mg	
12 noon		60 mg of aspirin
1:30 PM		Instructions and discharge
2 PM	60–100 mg	
5 PM	Instructions and discharge	
Day 2		
8 AM	100 mg	150 mg
11 AM	160 mg	325 mg
2 PM	325 mg	Instructions and discharge
5 PM	Instructions and discharge	

[a] Clinical and objective evaluation performed every 30 minutes and as needed.

[b] Provoking dose is repeated; symptoms are treated as indicated.

RESULTS

Patient Populations

One hundred twelve consecutive patients were referred for aspirin desensitization between 2007 and 2009. Ketorolac challenge and desensitization was conducted in 100 patients. Of the 12 patients not enrolled, the most common reason was nasal obstruction. Two patients declined because they did not like nasal sprays.

The 100 individuals in our control group were similar in their presentation for OAC and were challenged between 2003 and 2004 with routine and substantial use of montelukast, zafirlukast, and/or zileuton. In both groups, all patients were challenged with controlled asthma while taking standard asthma controller medications and avoiding antihistamines. No study participants were included in both groups.

Baseline Patient Clinical Characteristics

As indicated in Table 3, no statistical differences were found between the 2 groups with respect to age, sex, presence of nasal or sinus polyps, atopy, total number of upper and lower respiratory tract medications, hyposmia, or prior sinus operations. Mean (SD) baseline FEV_1 values were not significantly different (2.73 [0.8] L; range, 1.2–5.2 L) in the intranasal ketorolac and aspirin challenge group compared with the OAC group (2.87 $\pm$ 0.08 L; range, 1.2–5.8 L). The PNIF rate percentages were calculated only in the intranasal ketorolac and aspirin challenge group. Differences were found in the following categories: more patients were taking LTMDs in the intranasal ketorolac and aspirin challenge group (93% vs 77%; $P < .001$), fewer reported infections per year in the intranasal ketorolac and aspirin challenge group (2.8 vs 5.1; $P = .01$), and more patients with a history of asthma in the intranasal ketorolac and aspirin challenge group (97 vs 88; $P = .01$). Of the 100 patients in each group, 82 in the intranasal ketorolac and aspirin challenge group and 92 in the OAC group had a positive challenge result, met the diagnostic criteria for AERD, and were therefore included for further analysis.

Comparison of Intranasal Ketorolac and Aspirin Challenge and OAC Protocols

During challenge and desensitization, the average provoking dose of ketorolac was 12.1 mg, whereas 54.0 mg was the average provoking dose of aspirin in the OAC group. As indicated in Table 4, the PNIF rate decreased by an average of 28.7% in the intranasal ketorolac and aspirin challenge

Table 3. Baseline Patient Characteristics in the Intranasal Ketorolac and Aspirin Challenge and Oral Aspirin Challenge Groups

Characteristic	Intranasal ketorolac and aspirin challenge (n = 100)	Oral aspirin challenge (n = 100)	*P* value
Age, mean (SD) [range], y	51.1 (14.3) [18–73]	46.2 (12.7) [18–78]	0.17
No. of sinus infections per year, mean (SD) [range]	3.7 (3.9) [0–12]	5.1 (3.9) [0–12]	.01
No. of sinus operations, mean (SD) [range]	2.8 (2.5) [0–11]	2.9 (2.4) [0–13]	0.67
No. of medications, mean (SD) [range][a]	3.4 (1.3) [0–4]	3.3 (1.2) [0–4]	0.89
Smell score (0–4), mean (SD) [range]	1.0 (1.2) [0–4]	0.9 (1.3) [0–4]	0.45
Baseline FEV_1, mean (SD) [range], L	2.73 (0.8) [1.2–5.2]	2.87 (0.8) [1.2–5.8]	0.55
Baseline PNIF, mean (SD) [range], L/min	161.6 (44.8) [50–250]	NA	NA
Male, No. (%)	45 (45)	41 (41)	0.55
Atopy, No. (%)	71 (71)	66 (66)	0.76
History of nasal polyps, No. (%)	98 (98)	98 (98)	1.00
History of asthma, No. (%)	97 (97)	88 (88)	.01
LTMD use, No. (%)	93 (93)	77 (77)	.001
LTRA			
Montelukast	85	70	
Zafirlukast	3	6	
Zileuton	1	1	
Zileuton and montelukast	4	0	

Abbreviations: NA, not available; NS, not significant; FEV_1, forced expiratory volume in 1 second; PNIF, peak nasal inspiratory flow; LTMD, leukotriene modifier drug; LTRA, leukotriene receptor agonist.
[a] Any respiratory medications only (combined inhaled steroids and long-acting β_2-agonists counted as 2 medications).

group only; from baseline, a significant difference was seen in the maximum decrease in FEV_1 values during any part of the challenges (8.5 for intranasal ketorolac and aspirin challenge vs 13.4 for OAC; $P = .01$). Of the intranasal ketorolac and aspirin challenge patients, 65% experienced *only* a naso-ocular reaction compared with 38% in the OAC group ($P < .001$); this is defined as an upper respiratory tract reaction with change in FEV_1 of 15% or less. The duration to complete desensitization in the intranasal ketorolac and aspirin protocol was significantly less than the OAC, lasting 1.9 vs 2.6 days ($P < .001$). From a practical standpoint, 83% of the patients in the intranasal ketorolac and aspirin challenge group completed desensitization before the end of the second day compared with only 20% in the OAC group.

Adverse Reactions and Safety

In Table 5, bronchial reactions for 3 degrees of severity are presented. Individual patients in both groups experienced all degrees of severity in approximately the same percentages. The decrease in FEV_1 ranged from 0% to 53% in the intranasal ketorolac and aspirin challenge group and 0% to 55% in the OAC group. Treatment with standard inhaled bronchodilators was successful in treating ketorolac- or aspirin-induced bronchospasm. At the same time, there was a significant decrease in extrapulmonary adverse reactions during challenges in the intranasal ketorolac and aspirin challenge group (23% vs 45%; $P = .002$). More specifically, a higher percentage of patients in the OAC group experienced laryngospasm ($P = .02$) and gastrointestinal symptoms ($P = .001$) compared with the intranasal ketorolac and aspirin challenge group. These reactions were successfully managed with inhaled racemic or intramuscular epinephrine for laryngospasm and antacids, proton pump inhibitors, and intravenous ranitidine for gastrointestinal reactions.

No reactions were serious enough to warrant transfer to an emergency department or hospitalization in either study group. All reactions were treated in our outpatient clinic by experienced medical personnel.[9] Patients were discharged to home or a local hotel at the end of each clinic day.

Table 4. Intranasal Ketorolac and Aspirin vs Oral Aspirin Challenges

Positive for AERD	Intranasal ketorolac and aspirin challenge (n = 82)	Oral aspirin challenge (n = 92)	*P* value
PNIF, mean (SD), % decrease	28.7 (20.3)	NA	NA
FEV_1, mean (SD), % decrease	8.5 (12.2)	13.4 (12.4)	.01
Duration, mean (SD), d	1.9 (0.42)	2.6 (0.64)	<.001
Duration ≤2 days, No. (%)	68 (83)	18 (20)	<.001
Naso-ocular reaction only, No. (%)[a]	54 (65)	35 (38)	<.001

Abbreviations: AERD, aspirin-exacerbated respiratory disease; FEV_1, forced expiratory volume in 1 second; NA, not available; PNIF, peak nasal inspiratory flow.
[a] Change in FEV_1 of 15% or less.

Table 5. Types of Bronchial and Extrapulmonary Reactions

Reaction	Intranasal ketorolac and aspirin challenge, No. (%) (n = 82)	Oral aspirin challenge, No. (%) (n = 92)	*P* values
Bronchial (FEV_1 ≥15%)	26 (32)	35 (38)	0.61
15%–19%	11 (13)	12 (13)	0.66
20%–29%	8 (10)	13 (14)	0.63
≥30%	7 (9)	10 (11)	0.45
Extrapulmonary reactions	19 (23)	41 (45)	.002
Laryngospasm	6 (7)	17 (19)	.02
Gastrointestinal[a]	10 (12)	30 (33)	.001
Cutaneous[b]	5 (6)	9 (10)	0.78

Abbreviations: FEV_1, forced expiratory volume in 1 second; NS, nonsignficant.
[a] Nausea, vomiting, gastric pain, or heartburn.
[b] Urticaria, angioedema, pruritus, and erythema.

Subanalysis of the Ketorolac Desensitized Group

Of the 82 patients who completed the intranasal ketorolac and aspirin challenge, during the ketorolac challenges, 74 (90%) experienced positive reactions (defined as rhinitis, conjunctivitis, and/or bronchospasm with a significant decrease in PNIF rate of ≥20% and/or FEV_1 values ≥15%). Eight patients (10%) had no reactions during intranasal ketorolac challenges but then had respiratory reactions during the OAC portion of the protocol. Of the 74 patients who reacted to ketorolac, 49 (66%) subsequently completed the protocol with no further reactions to the oral aspirin portion of the challenge and desensitization. The remaining 25 patients (34%) experienced some degree of reactions during the oral aspirin portion of the protocol. However, it is important to emphasize that 14 of those 25 patients (56%) had their dominant reaction during the intranasal ketorolac portion of their challenges and subsequently had only mild naso-ocular or bronchial reactions during their oral aspirin protocol. Therefore, 63 reactors (77%) were completely or mainly desensitized during the intranasal ketorolac portion of the challenge sequence.

DISCUSSION

This is the first study, to our knowledge, to evaluate and compare the use of intranasal ketorolac for desensitization in AERD. Our control group, which had previously undergone standard OAC, was well matched, even though oral aspirin desensitization was conducted several years earlier. As indicated in Table 3, the important characteristics of a group of patients with AERD were similar as were their baseline lung function values. There were a few differences, such as more frequent use of LTMDs in the intranasal ketorolac and aspirin group; however, this finding correlates with the significantly higher number of patients with asthma in that group.[10–12] Otherwise, aside from more sinus infections per year reported in the OAC group, the characteristics of each group were similar and well matched.

In the intranasal ketorolac and aspirin group, 90% of the patients challenged with intranasal ketorolac had a respiratory reaction and were primarily desensitized during the ketorolac portion of the protocol, allowing us to more rapidly advance to higher doses of oral aspirin. Hope et al[7] recently published an approach to aspirin dosing with a streamlined method of oral aspirin dosing, starting at 30 to 45 mg and incrementally increasing the dose at 3-hour intervals to 45, 60, 100, 150, and 325 mg during 3 days, depending on treatment of reactions and the necessity of repeating doses. In this sequence of dosing, the mathematically shortest time to achieve desensitization with OAC required 2 days, including a 3-hour wait after 325 mg of aspirin. Experiencing any reaction along the way automatically requires treatment and repeat dosing, which drives the process into the third or even fourth day. This is what we observed in our OAC control group, in which the mean time to completion of desensitization was 2.48 days and only 18% of the patients completed desensitization before the close of day 2. By contrast, intranasal ketorolac and aspirin desensitization was significantly shorter, in which the mean time was 1.9 days and 83% of the patients completed desensitization by the end of day 2. This finding has practical value because 1 of the impediments to aspirin desensitization is time to completion and increasing costs with each additional day.

The other significant advantage of intranasal ketorolac and aspirin was fewer asthma symptoms during any part of the challenges. Although both groups had similar ranges of decrease in FEV_1, the average decrease was less with intranasal ketorolac and aspirin. We had 1 recalcitrant patient from the intranasal ketorolac and aspirin group whose FEV_1 decreased 53% during intranasal ketorolac and aspirin challenge and time to completion of desensitization was 5 days. Six other patients had FEV_1 values that decreased by more than 30% during some phase of the challenge or desensitization, and desensitization was completed in 3 to 4 days. As indicated in Table 5, the percentage of those who experienced various degrees of significant bronchospasm (>15%) was not statistically different from the OAC group.

During both intranasal ketorolac and aspirin challenge and OAC, some patients experienced adverse extrapulmonary effects, such as laryngospasm, gastric symptoms, or cutaneous reactions. These were significantly fewer in the intranasal

ketorolac and aspirin group. This is 1 reason why desensitization could be completed so quickly in the intranasal ketorolac and aspirin group because extrapulmonary complications always require treatment and delay. Intranasal ketorolac and aspirin treatment is applied locally to the nasal membranes, thus theoretically localizing the reaction to the airways.

Although aspirin desensitization has been shown to be relatively safe as discussed by Williams et al,[13] the greatest barrier to aspirin desensitization continues to be concerns of life-threatening reactions and the time required to complete standard OAC protocols. Between 30% and 42% of asthmatic patients with nasal polyps, who are avoiding or have never taken an nonsteroidal anti-inflammatory drug, actually have AERD.[14,15] Yet, for the most part, these patients' conditions remain undiagnosed until the patients ingest full therapeutic doses of a nonsteroidal anti-inflammatory drug and experience bronchospasm. If in 2 days, asthmatic patients with nasal polyps could be cleared of having AERD with a negative ketorolac or modified aspirin challenge result (approximately two-thirds of the time) or diagnosed as having the disease and desensitized to aspirin, this would be a great improvement over current practices. Our novel method of combining nasal ketorolac challenge and OAC might help clinicians resolve this conundrum and also provide a safe and rapid method for desensitizing history-positive patients suspected of having AERD. However, to use intranasal ketorolac and aspirin challenge, patients would need a polypectomy (either medical or surgical) to clear the nasal passages so that the procedure can be performed. It is our policy to recommend scheduling aspirin desensitization approximately 1 month after sinus and polyp surgery because our best outcomes are achieved in individuals who have clear sinuses at the time of desensitization. Nine of our patients were not eligible for intranasal ketorolac and aspirin challenge because of nasal obstruction from polyps.

In conclusion, use of intranasal ketorolac combined with OACs is an effective and well-tolerated protocol for desensitization in AERD. On the basis of our study, it is safer and less time-consuming than standard oral aspirin protocols.

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